# CHEMICAL CONSTITUTION AND ACTIVITY OF BIPYRIDYLIUM HERBICIDES

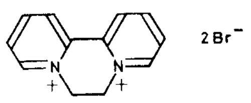
## IV.*—Diquaternary salts of methyl substituted 1,10-phenanthrolines

By J. E. DICKESON and L. A. SUMMERS

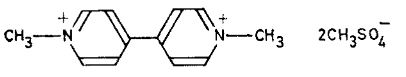
Eight bridged diquaternary salts of methyl substituted 1,10-phenanthrolines have been prepared. They are reduced in aqueous solution to radical cations at about the same potential as diquat by a one electron transfer which is largely reversed by air. In herbicidal tests they showed slight activity at a rate equivalent to 8 lb/acre. Their relatively poor phytotoxic properties are considered to be due to their large size which hinders their reaching the site of biological action of the bipyridylium herbicides.

### Introduction

The bipyridylium herbicides, especially diquat (**I**) and paraquat (**II**), have attracted much attention and have been the subject of numerous reports.[1–18] Their mode of action is thought to be connected with their ability to be rapidly reduced in aqueous solution to stable radical cations (e.g. **III**) at a potential ($E_0$) of $\sim -0{\cdot}35$ to $-0{\cdot}45$ volts by a one electron transfer which is rapidly and quantitatively reversed by oxygen. The stability of the radical cations is due to the delocalisation of the odd electron over both pyridine rings which are essentially co-planar.



(I)



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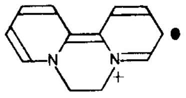
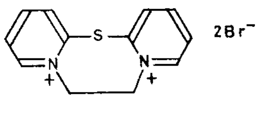


(III)

In work reported in earlier parts of this series and in related papers evidence has accumulated which substantially supports this theory. For instance, the introduction of a sulphur bridge between the pyridine rings of diquat to give compound **IV** resulted in loss of herbicidal activity,[19–22] a finding which is consistent with the theory of the mode of action of diquat and paraquat since, compound **IV** was reduced to a rather unstable radical cation (cf. Hünig[23]), presumably because it is unlikely to be planar. The dimethiodide of 2,2′-bipyridyl which also is not planar was reduced to a fairly stable radical cation[24] but at a very low potential, and it too was inactive as a herbicide.[2] Diquaternary salts of a number of planar hetero-aromatic systems have also been studied. A 1,5-naphthyridine salt, (**V**), gave a stable radical but the reduction potential was about $+0{\cdot}02$ volts and the salt was largely present in a pseudo-base form at physiological pH values. Not unexpectedly, therefore, it was inactive.[25,26] The fully aromatic analogue of diquat,[27,28] compound **VI**, and the polymethylene-bridged diquaternary salts of 1,10-phenanthroline,[29–31] compounds **VII** ($R'=R''=H$) and **VIII** ($R'=R''=H$) however, were reduced to stable radical cations at a potential of $\sim -0{\cdot}27$ volts although the one electron transfer was not quite quantitatively reversed by air. They showed appreciable herbicidal activity (see Table I) but they were not as active as diquat possibly because of their higher reduction potentials. The related salts **IX** and **X** gave unstable radicals, probably because of their greater chemical reactivity, and were inactive as herbicides.[32,33]



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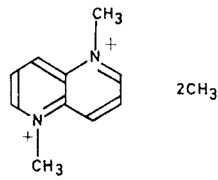

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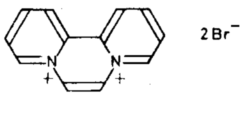

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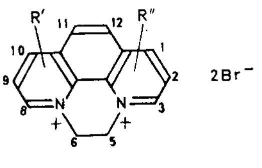

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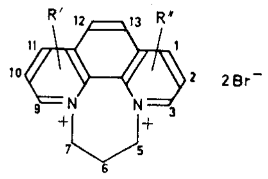

(VIII)

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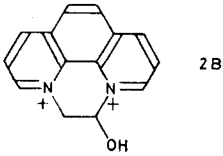
* Part III, *Tetrahedron*, 1968, **24**, 6453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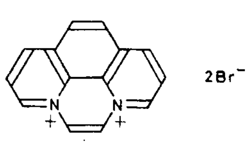
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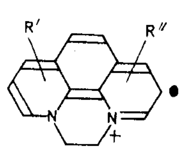
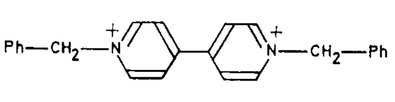
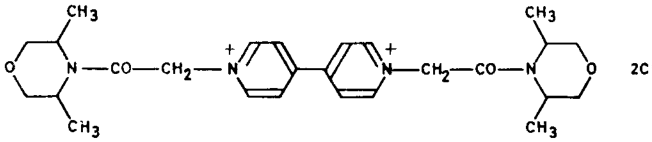

(XI)


(XII)

While the ability to be reversibly reduced at appropriate potentials to stable radical cations is almost certainly involved in the phytotoxic process with bipyridylium herbicides, there are indications that other factors, especially size, are also important in determining whether a compound possesses herbicidal properties. For example, the benzyl viologen di-cation, (XII)[2,9] which contains long alkyl quaternising groups and diquaternary salts of phenyl-substituted 4,4′-bipyridyls[34] are inactive although they meet the other requirements thought to be necessary for herbicidal activity. The herbicidal activity of compounds of the morfamquat (XIII) type[11,35] is presumably accounted for by hydrolysis of their long carbamoyl quaternising groups to small chains *in vivo*.

In view of the phytotoxicity of the phenanthroline salts VII ($R'=R''=H$) and VIII ($R'=R''=H$), the present investigations are extended to diquaternary salts of 1,10-phenanthrolines containing electron-releasing methyl substituents in order to study compounds with reduction potentials closer to that of diquat.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## Experimental and Results

### Preparation of compounds VII and VIII

The diquaternary salts, 5,6-dihydropyrazino [1,2,3,4-*lmn*]-1, 10-phenanthrolinium dibromides (VII) and 5H-6,7-dihydro-1,4-diazepino[1,2,3,4-*lmn*]-1,10-phenanthrolinium dibromides (VIII) (see Table II) were prepared by treating the appropriate 1,10-phenanthroline with boiling ethylene dibromide or 1,3-dibromopropane for 30–60 min. The precipitate which was obtained was crystallised from aqueous ethanol to give the products in 50–80% yield. Ultra-violet absorption spectra were taken with 0·0001 M solutions in water (Table II). Elemental micro-analyses were in agreement with the structures proposed.

TABLE I

**Herbicidal tests on diquaternary salts of 1,10-phenanthroline and related compounds**

| Compound | R′ | R″ | Activity Rating | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Pre-emergence | | | | | | Post-emergence | | | | | |
| | | | Peas | Mustard | Barley | Maize | Lin-seed | Ryegrass | Linseed | Buck-wheat | Mustard | Peas | Sugar-beet | Barley |
| **I** | | | 3 | 4 | 3 | 3 | 3 | 4 | 9 | 7 | 10 | 7 | 7 | 7 |
| **IV** | | | 1 | 2 | 1 | 0 | 0 | 0 | 5 | 5 | 4 | 4 | 5 | 4 |
| **VII** | H | H | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| **VIII** | H | H | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 3 | 2 |
| **VII** | 11-Me | H | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **VIII** | 12-Me | H | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 |
| **VII** | 11-Me | 12-Me | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| **VIII** | 12-Me | 13-Me | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| **VII** | 1-Me | 10-Me | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| **VIII** | 1-Me | 11-Me | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 |
| **VII** | 3-Me | 8-Me | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **VIII** | 3-Me | 9-Me | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |

TABLE II

**Ultra-violet absorption spectra of diquaternary salts of methyl substituted 1,10-phenanthrolines**

| Formula | R′ | R″ | M.p.°C | $\lambda_{max}$, nm | log $\epsilon$ | $E_0$, volts |
|---|---|---|---|---|---|---|
| **VII** | 11-Me | H | >350 | 231, 278,* 288, 305,* 317 | 4·40, 4·39, 4·56, 3·82, 3·86 | −0·29 |
| **VII** | 11-Me | 12-Me | >350 | 235,* 246,* 286,* 295, 311, 324 | 4·31, 4·23, 4·41, 4·54, 3·82, 3·80 | −0·32 |
| **VII** | 1-Me | 10-Me | >350 | 227,* 274, 282, 298,* 313 | 4·37, 4·58, 4·65, 3·90, 3·68 | −0·41 |
| **VII** | 3-Me | 8-Me | >350 | 231, 272,* 284, 303, 314, 329 | 4·37, 4·40, 4·53, 3·87, 3·93, 3·98 | −0·37 |
| **VIII** | 12-Me | H | 271† | 232, 282,* 291, 311,* 323 | 4·39, 4·41, 4·53, 3·80, 3·69 | −0·28 |
| **VIII** | 12-Me | 13-Me | >350 | 237, 292,* 299, 323,* 327* | 4·32, 4·42, 4·49, 3·72, 3·73 | −0·31 |
| **VIII** | 1-Me | 11-Me | 320† | 234, 276,* 285, 304,* 315 | 4·13, 4·37, 4·54, 3·65, 3·65 | −0·42 |
| **VIII** | 3-Me | 9-Me | 307† | 230,* 275,* 287, 320, 333 | 4·26, 4·24, 4·37, 3·77, 3·77 | −0·35 |

* Shoulder
† With decomposition

**Reduction experiments**

All the diquaternary salts listed behaved essentially as described[29-31] for the unsubstituted phenanthroline salts **VII** (R′=R″=H) and **VIII** (R′=R″=H), on reduction with zinc dust and in polarograph experiments. In aqueous solution on treatment with zinc dust they immediately developed an intense deep red or violet coloration which is attributed to the corresponding radical cation (e.g. **XI**). When the reducing agent was removed and the solution was shaken for about 15–60 seconds in air the deep colour substantially discharged and the original diquaternary salt was largely (~ 90%), but not quantitatively, regenerated (u.v. evidence). Results obtained from polarography were consistent with the uptake of one electron by the salts. They give a typical symmetrical one electron reduction wave with a half-wave potential in the range −0·28 to −0·42 volts independent of pH and concentration. Like the unsubstituted diquaternary salts they did not give a clear-cut second reduction wave (see examples in Fig. 1). Diquat dibromide (**I**) was included in the polarograph experiments for comparison and gave, as before,[21] two distinct one electron reduction steps with $E_0$ values of −0·36 and ~ −0·70 volts respectively. It is apparent from these results that the diquaternary salts of the methyl substituted 1,10-phenanthrolines are rapidly reduced in aqueous solution to stable radical cations at about the same potential as diquat and that the one electron transfer is largely reversed by atmospheric oxidation (cf. Ref. 37).

The polarograph experiments were carried out as before[21,22,24,30,31,33] on 0·001 M and 0·0015 M aqueous solutions at 20° in Britton and Robinson or Sorensen buffers of pH 4·6, 5·0, 5·9, 6·8, 7·4, 8·0, and 8·7 using a standard calomel electrode. The half-wave potentials (see Table II) were assumed to be $E_0$ values and were calculated by adding 0·25 volts to the $E_{\frac{1}{2}}$ values. Experimental error was ± 0·02 volts.

**Herbicidal tests**

The compounds listed in Table II were examined in pre- and post-emergent herbicidal tests (Table I). The aromatic analogue of diquat (**VI**)[27,28] and the diquaternary salts **VII** (R′=R″=H) and **VIII** (R′=R″=H) of 1,10-phenanthroline[29-31] which had previously been found to be active in preliminary tests[27,30] were included for comparison along with diquat dibromide (**I**).

The chemicals were assayed as aqueous solutions in the glasshouse against six plant species at an initial application rate of 8 lb/acre. The effectiveness of a compound against each species was rated 21 days (pre-emergence) or 7 days (post-emergence) after application on a scale 0–10, where 0 represents no effect and 10 represents complete kill. Compounds scoring 8 or more on this scale against any one species were re-assayed against all species at lower application rates of 4 lb/acre, 2 lb/acre, 1 lb/acre, etc. until no assay rating exceeded 7. The assay data were then translated into an activity rating for each species as follows:

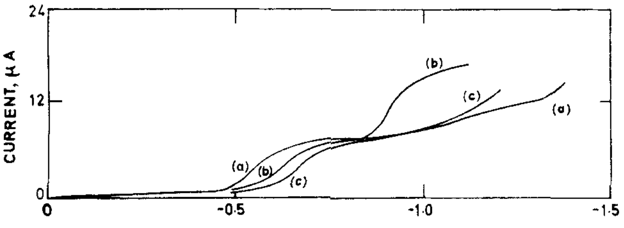

FIG. 1. *Polarograms at pH* 4·6

(a) 5,6-dihydro-11-methylpyrazino-[1,2,3,4-*lmn*]-1,10-phenanthrolinium dibromide (VII; R′=11–Me, R″=H); (b) diquat dibromide (I); (c) 5,6-dihydro-1,10, dimethylpyrazino[1,2,3,4-*lmn*]-1,10-phenanthrolinium dibromide (VII; R′=1–Me, R″=10–Me)

| Assay rating | Activity Rating |
|---|---|
| < 8 at 8 lb/acre | 0 |
| > 8 at 8 lb/acre | 1 |
| > 8 at 4 lb/acre | 2 |
| > 8 at 2 lb/acre | 3 |
| > 8 at 1 lb/acre | 4 |
| > 8 at 8 oz/acre | 5 |
| > 8 at 4 oz/acre | 6 |
| > 8 at 2 oz/acre | 7 |
| > 8 at 1 oz/acre | 8 |
| > 8 at 0·5 oz/acre | 9 |
| > 8 at 0·25 oz/acre | 10 |

In the post-emergent tests diquat dibromide (**I**), its aromatic analogue, (**VI**) and the unsubstituted salts **VII** (R′=R″=H) and **VIII** (R′=R″=H) desiccated green plant tissue rapidly. The methyl substituted phenanthroline salts, however, were generally slower acting. In some cases their herbicidal action consisted of a blackening rather than a desiccating action and the plants frequently outgrew these effects.

As expected the compounds were less active in pre-emergent than in the post-emergent tests due to the absorption of the salts on soil constituents.

## Discussion

The biological results in Table I show that diquat dibromide (**I**), is the most active of the compounds tested. In the post-emergent assays the aromatic analogue of diquat, compound **VI**, (cf. Refs. 27, 28) was very active at rates as low as 8 oz/acre against some plant species and the unsubstituted phenanthroline salts (cf. Refs. 30, 31), compounds **VII** (R′=R″=H) and **VIII** (R′=R″=H), at 4 and 8 lb/acre. The methyl substituted phenanthrolines, however, showed no improvement in activity over the unsubstituted analogues and were usually inferior.

All the compounds listed in Table I are reduced in aqueous solution to stable radical cations in the potential range ($E_0$) −0·27 to −0·42 volts. Only in the case of diquat is the one-electron transfer completely reversible, although with the other compounds it is almost completely reversible. This difference may account for the greater herbicidal activity of diquat since continual regeneration of the diquaternary salt from its radical cation is thought to be an important part of the herbicidal process.[13] However other factors must also be considered to explain the results in Table I. The reduction potential and the size of the compounds are almost certainly involved. The redox potential of diquat is −0·35 volts and of paraquat −0·45 volts.[2] These potentials are very close to those of pyridine nucleotides and ferredoxin (~ −0·32 to −0·43 volts) which are intimately involved in electron transfer mechanisms in photosynthesis,[36] a process clearly disrupted by the bipyridylium herbicides. It may be that a potential lower than −0·32 volts is necessary for outstanding phytotoxic effects and this would account for the lower activity of compounds **VI**, **VII**, ($R'=R''=H$) and **VIII** ($R'=R''=H$) which have reduction potentials of about −0·27 volts.[27,30] It does not explain, however, the poor activity of the methyl substituted phenanthroline salts which have $E_0$ values close to that of diquat. The size of the molecule apparently influences herbicidal effectiveness. The methyl substituted phenanthroline salts are bigger molecules than the unsubstituted salts and are much larger than diquat and its aromatic analogue. It may well be that they have difficulty in reaching the site of biological action of the bipyridylium herbicides. This suggestion is supported by the observation that they are slower acting than diquat and paraquat and by the report of the lack of herbicidal activity shown by the large benzyl viologen dication (**XII**)[2,9] and phenyl substituted 4,4′-bipyridyl salts[34] which also are reversible one electron transfer systems of potential.

## Conclusion

These results support the theory of Homer *et al.*[2] that for herbicidal activity of the type associated with diquat and paraquat the compounds must be capable of being reduced in aqueous solution at appropriate potentials (~ −0·35 to −0·45 volts) to stable radical cations which are reversibly oxidised by air. The evidence suggests that a reduction potential lower than −0·27 volts may be necessary for outstanding herbicidal effects. While one-electron transfer properties are almost certainly involved in the herbicidal process further evidence has been obtained which indicates that the size of the molecule is a very important factor in determining whether a compound possesses good herbicidal activity.

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## References

1. Stubbs, J., *Outl. Agric.*, 1958, **2**, 64
2. Homer, R. F., Mees, G. C., & Tomlinson, T. E., *J. Sci. Fd Agric.*, 1960, **11**, 309
3. Calderbank, A., *Agric. vet. Chem.*, 1960, **1**, 197
4. Cronshey, J. F. H., *Weed Res.*, 1961, **1**, 68
5. Calderbank, A., & Crowdy, S. H., *Rep. Prog. appl. Chem.*, 1962, **47**, 536
6. Jeater, R. S. L., *Agric. vet. Chem.*, 1963, **4**, 20
7. Austin, W. G. L., *Outl. Agric.*, 1963, **4**, 35
8. Boon, W. R., *Outl. Agric.*, 1964, **4**, 163
9. Boon, W. R., *Chemy Ind.*, 1965, p. 782
10. Brian, R. C., *Chemy Ind.*, 1965, p. 1955
11. Heywood, B. J., *Rep. Prog. appl. Chem.*, 1964, **49**, 360; 1965, **50**, 232
12. Hood, A. E. M., *Outl. Agric.*, 1965, **4**, 286
13. Calderbank, A., *Biochem. J.*, 1966, **101**, 2P
14. Calderbank, A., & Slade, P., *Outl. Agric.*, 1966, **5**, 55
15. Boon, W. R., *Endeavour*, 1967, **26**, 27
16. Moreland, D. E., *A. Rev. Pl. Physiol.*, 1967., **18**, 365
17. Funderburk, H. H., & Bozarth, G. A., *J. agric. Fd Chem.*, 1967, **15**, 563
18. Allen, H. P., *Outl Agric.*, 1967, **5**, 149
19. Summers, L. A., *Angew. Chem.*, 1966, **78**, 644; *Angew. Chem. Int. Edn.*, 1966, **5**, 605
20. Summers, L. A., *Chem. Commun.*, 1966, p. 546
21. Summers, L. A., *Nature, Lond.*, 1967, **214**, 381
22. Summers, L. A., *Tetrahedron*, 1968, **24**, 2697
23. Hünig, S., *Pure appl. Chem.*, 1967, **15**, 109
24. Summers, L. A., *Naturwissenschaften*, 1967, **54**, 491
25. Summers, L. A., & Dickeson, J. E., *Chem. Commun.*, 1967, p. 1183
26. Summers, L. A., *Aust. J. Pharm. Sci. Supp.*, 1968, **49**, No. 63
27. Summers, L. A., & Black, A. L., *Nature, Lond.*, 1968, **218**, 1067
28. Black, A. L., & Summers, L. A., *J. chem. Soc.*, in the press
29. Summers, L. A., & Pickles, V. A., *Chemy Ind.*, 1967, p. 619
30. Summers, L. A., *Nature, Lond.*, 1967, **215**, 1410
31. Summers, L. A., *Tetrahedron*, 1968, **24**, 5433
32. Black, A. L., Summers, L. A., & Pickles, V. A., *Chemy Ind.*, 1967, p. 1836
33. Black, A. L., & Summers, L. A., *Tetrahedron*, 1968, **24**, 6453
34. Downes, J. E., *J. chem. Soc.* (C), 1967, p. 1491
35. Fox, H. M., *Proc. Seventh Br. Weed Control Conf., Glasgow*, 1964, p. 29
36. Black, C. C., & Myers, L., *Weeds*, 1966, **14**, 331
37. Hünig, S., & Gross, J., *Tetrahedron Lett.*, 1968, p. 2599